WHAT IS CLAIMED IS:

1. A method for producing a xenogeneic immunoglobulin or analog thereof in a non-human animal host, said method comprising:

immunizing said host with an immunogen under conditions to stimulate an immune response to said immunogen, whereby said host mounts an immune response to said immunogen and produces B-cells producing immunoglobulin specific for said immunogen, and isolating xenogeneic immunoglobulin produced bys aid host,

wherein said host is characterized by 1) being substantially incapable of producing endogenous immunoglobulin heavy chain; (2) being substantially incapable of producing endogenous immunoglobulin light chains; and 3) being capable of producing a xenogeneic immunoglobulin or analog thereof.

2. A method according to Claim 1, wherein said host is rendered substantially incapable of producing endogenous immunoglobulin heavy and light chains by inactivation of at least a portion of said endogenous immunoglobulin heavy and light chain loci by homologous recombination.

3. A method according to Claim 2, wherein said inactivation is a result of introduction of a lesion into the endogenous immunoglobulin loci.

4. A method according to Claim 1, wherein said analog comprises a variable region joined by a peptide bond to a peptide other than solely the immunoglobulin constant region.

5. A method according to Claim 1, wherein said xenogeneic immunoglobulin is human immunoglobulin.

6. A method according to Claim 1, including the additional step of immortalizing said B-cells.

7. A method according to Claim 1, wherein said host comprises B-cells comprising a functional immunoglobulin locus comprising a xenogeneic variable region and at least one human constant region.

8. A method according to Claim 1, wherein said non-human host is a rodent.

9. A method according to Claim 1, wherein said xenogeneic immunoglobulin is chimeric immunoglobulin.

10. A method according to Claim 9, wherein said chimeric immunoglobulin is mouse/human immmunoglobulin.

11. An immortalized non-human cell line genetically modified so as to lack the ability to produce immunoglobulin endogenous to the cell line and comprising xenogeneic immunoglobulin loci encoding at least one xenogeneic immunoglobulin heavy chain and a light chain;

wherein said xenogeneic immunoglobulin heavy and light chain loci are expressed.

12. An immortalized cell line according to Claim 11, wherein said cell line is a B cell hybridoma.

13. An immortalized cell line according to Claim 11, wherein said non-human cell line is a murine cell line, and said xenogeneic immunoglobulin loci are human immunoglobulin loci.

14. A method of making a xenogeneic immunoglobulin comprising culturing the immortalized cell line of Claim 11 under suitable culture conditions and recovering the xenogeneic immunoglobulin.

15. A xenogeneic immunoglobulin produced by the method according to Claim 1 or 14.

16. A genetically modified non-human animal comprising a modified genome selected from the group consisting of:

a genome heterozygous or homozygous for a modification that results in the inability of at least one locus to produce endogenous immunoglobulin heavy or light chains;

a genome heterozygous or homozygous for a modification that results in the inability of at least one locus to produce endogenous immunoglobulin heavy and light chains;

a genome heterozygous for a modification that results in the inability of at least one locus to produce endogenous immunoglobulin heavy and light chains and hemizygous for the ability to produce xenogeneic immunoglobulin heavy chains;

a genome heterozygous for a modification that results in the inability of at least one locus to produce endogenous immunoglobulin heavy and light chains and hemizygous for the ability to produce xenogeneic immunoglobulin light chains;

a genome homozygous for a modification that results in the inability to produce endogenous immunoglobulin heavy and light chains and homozygous for the ability to produce xenogeneic immunoglobulin heavy or light chains;

a genome homozygyous for a modification that results in the inability to produce endogenous immunoglobulin heavy and light chains and hemizygous for the ability to produce xenogeneic immunoglobulin heavy or light chains;

a genome homozygous or heterozygous for a modification that results in the inability of at least one locus to produce endogenous immunoglobulin heavy and light chains and hemizygous for the ability to produce xenogeneic immunoglobulin heavy and light chains;

a genome heterozygous for a modification that results in the inability of at least one locus to produce endogenous immunoglobulin heavy or light chain and hemizygous for a modification that results in the ability to produce xenogeneic immunoglobulin heavy and light chains;

a genome homozygous for a modification that results in the inability to produce endogenous immunoglobulin heavy or light chain and homozygous for a modification that results in the ability to produce xenogeneic immunoglobulin heavy and light chains; and

a genome homozygous for a modificatio that results in the inability to produce endogenous immunoglobulin heavy or light chain and hemizygous for a modification that results in the ability to produce xenogeneic immunoglobulin heavy and light chains.

17. A non-human animal according to Claim 16, wherein the animal is murine.

18. A non-human animal according to Claim 16, wherein the xenogeneic immunoglobulin is human.

19. A non-human animal according to Claim 16, wherein the inability to produce endogenous immunoglobulin is a result of inactivation of at least a portion of the endogenous immunoglobulin loci by homologous recombination.

20. A non-human animal according to Claim 19, wherein at least a portion of the endogenous immunoglobulin light and heavy chain loci are replaced with at least one locus capable of producing xenogeneic immunoglobulin.

21. A non-human animal according to Claim 16, wherein said inactivation comprises introduction of a lesion in the loci encoding said heavy and/or light immunoglobulin chains.

22. A non-human animal according to Claim 21, wherein said lesion is in the constant and/or J region.

23. A non-human animal according to Claim 21, wherein said light chain loci are kappa immunoglobulin chain loci.

24. A non-human animal according to Claim 21, wherein said light chain loci are lambda immunoglobulin chain loci.

25. A transgenic murine animal comprising a genome lacking the ability to produce endogenous immunoglobulin, said genome comprising a lesion in the J region of the heavy chain immunoglobulin loci, and a lesion in the constant and/or J regions of the light chain immunoglobulin loci.

26. A murine animal according to Claim 25, wherein said genome further comprises xenogeneic heavy and light chain immunoglobulin loci and said murine animal has the ability to produce xenogeneic immunoglobulin.

27. A method for producing a modified non-human animal, said animal having a xenogeneic DNA segment of at least 100 kb stably integrated into the genome of said animal, said method comprising:

combining under fusing conditions yeast spheroplasts, said spheroplasts comprising a YAC having said xenogeneic DNA segment and a marker for selection, with embryonic stem cells of said animal, whereby said xenogeneic DNA segment becomes integrated into the genome of said embryonic stem cells;

selecting for embryonic stem cells carrying said xenogeneic DNA segment by means of the marker;

transferring said embryonic cells into a host blastocyst and implanting said blastocyst in a pseudopregnant animal recipient, and allowing said blastocyst to develope to term to produce a chimeric animal carrying said xenogeneic DNA segment; and

mating said chimeric animal with an animal of the same species to produce said modified animal carrying said xenogeneic DNA segment.

28. A method according to Claim 27, wherein said marker is the HPRT gene and said embryonic stem cell is HPRT deficient.

29. A method according to Claim 27, wherein said step of mating produces heterozygous progeny and the heterozygous progeny are mated to produce homozygous progeny.

30. A method according to Claim 27, wherein said animal is a rodent.

31. A method according to Claim 30, wherein said animal is a murine animal.

32. A method according to Claim 27, wherein said xenogeneic DNA is human DNA.

33. A method according to Claim 32, wherein said xenogeneic DNA is human immunoglobulin DNA in substantially intact form.

34. The modified animal produced by the method according to Claim 27.

35. A non-human animal heterozygous or homozygous for a xenogeneic genomic mammalian DNA segment of at least 100 kb, stably integrated in substantially intact form into the genome of said animal.

36. A non-human animal according to Claim 35, comprising a HPRT gene and wherein said xenogeneic DNA is human DNA.

37. A non-human animal according to Claim 36, wherein said human DNA is human immunoglobulin DNA in substantially intact form.

38. A non-human animal according to Claim 35, wherein said animal is a rodent.

39. A non-human animal according to Claim 38, wherein said animal is a murine animal.

40. An embryonic stem cell comprising a genome having endogenous immunoglobulin heavy chain loci, and immunoglobulin light chain loci, said genome comprising a lesion in said endogenous immunoglobulin heavy chain and/or light loci, resulting in the incapacity of the immunoglobulin locus comprising said lesion to rearrange.

41. An embryonic stem cell according to Claim 40, wherein said lesion is in the J and/or constant regions of said endogenous immunoglobulin loci.

42. An embryonic stem cell according to Claim 40, wherein said lesion is insertion of a xenogeneic sequence.

43. An embryonic stem cell according to Claim 42 wherein said xenogeneic sequence is immunoglobulin DNA or a selectable marker.

44. An embryonic stem cell according to Claim 43, wherein said marker is neomycin.

45. An embryonic stem cell according to Claim 42, wherein said lesion further comprises deletion of endogenous immunoglobulin DNA.

46. An embryonic stem cell according to Claim 40 wherein said stem cell is homozygous for the lesion.

47. An embryonic stem cell according to Claim 40 wherein the lesion is in the heavy chain immunoglobulin J region loci.

48. An embryonic stem cell according to Claim 40 wherein the lesion is in the light chain immunoglobulin J region loci.

49. An embryonic stem cell according to Claim 40 wherein said lesion comprises replacement of at least a portion of the immunoglobulin light and heavy chain loci comprising said endogenous immunoglobulin loci with loci capable of producing xenogeneic immunoglobulin by homologous recombination.

50. A murine embryonic stem cell comprising homozygotic alleles of immunoglobulin heavy chain loci, said loci comprising a lesion resulting in the incapacity of the immunoglobulin loci comprising said lesion to rearrange.

51. A murine embryonic stem cell according to Claim 50, wherein said lesion is in the J region of said immunoglobulin heavy chain loci.

52. A murine embryonic stem cell comprising homozygotic alleles of immunoglobulin light chain loci, said loci comprising a lesion resulting in the incapacity of the immunoglobulin loci comprising said lesion to rearrange.

53. A murine embryonic stem cell according to Claim 52, wherein said lesion is in the constant and/or J regions of said immunoglobulin light chain loci.

54. A murine embryonic stem cell of a murine host said stem cell comprising a genome having immunoglobulin loci comprising J regions, said stem cell comprising a lesion in at least one of the J regions of the immunoglobulin locus resulting in the incapacity of said immunoglobulin locus to rearrange, said embryonic stem cell produced by the method comprising introducing homologous DNA into a murine stem cell in culture, wherein said homologous DNA comprises a region homologous with the J region of an immunoglobulin locus and a marker gene for insertion into said locus; and selecting for embryonic stem cells having undergone homologous recombination with said homologous DNA.

55. A murine embryonic stem cell according to Claim 54 wherein said marker is the neomycin gene.

56. A murine embryonic stem cell according to Claim 54 wherein said lesion is in at least one of the J regions of an endogenous heavy chain immunoglobulin locus.

57. A murine embryonic stem cell comprising at least 100 kb of xenogeneic DNA.

58. A murine embryonic stem cell according to Claim 57, wherein said xenogeneic DNA is immunoglobulin heavy and/or light chain immunoglobulin DNA.

59. A murine embryonic stem cell according to Claim 58, wherein said xenogeneic DNA is human immunoglobulin DNA in substantially intact form.

60. A method for modifying a genome of a recipient murine embryonic stem cell by homologous recombination with a large xenogeneic DNA genomic fragment previously manipulated in a yeast artificial chromosome (YAC), the improvement which comprises:

introducing at least one YAC into said murine embryonic stem cell by spheroplast fusion, and selecting recipient cells comprising said genomic fragment, wherein said YAC comprises a mammalian selectable or screenable gene, wherein said YAC is faithfully transmitted through the host germline, and said xenogeneic DNA fragment is transmitted in substantially intact form.

61. A method according to Claim 60, wherein said selectable or screenable gene is HPRT and the recipient cells are selected with HAT medium and are negative for HPRT.

62. A method according to Claim 60, wherein said selectable or screenable gene is a HPRT minigene.

63. A method according to Claim 60 wherein said selectable or screenable gene is cDNA encoding a gene selected from the group consisting of neomycin, hygromycin, HPRT, GPT and βgal.

64. A method according to Claim 60, wherein said YAC comprises at least 100 kb of a human immunoglobulin DNA locus in substantially intact form.

65. A modified YAC according to Claim 64, further comprising a mammalian selectable or screenable marker.

66. A modified YAC according to Claim 65, wherein the selectable marker is HPRT.

67. A murine embryonic stem cell comprising a genome modified according to the method of Claim 60.

68. A murine animal heterozygous for a xenogeneic unrearranged mammalian DNA segment of at least 100 kb stably integrated into the genome of said murine animal.

69. A murine animal according to Claim 68 comprising a xenogeneic HPRT gene and wherein said DNA segment is human immunoglobulin.

70. A human antibody molecule characterized by;
comprising the protein sequences of the human immunoglobulin heavy and light chains;
specificity for an immunogen; and
having other than human glycosylation.

71. A human antibody molecule according to Claim 70, wherein said antibody is monoclonal.

72. A method for producing a genetically modified non-human animal, comprising interbreeding a first parent and a second parent, and recovering the progeny thereof, wherein the parents and progeny are selected from the group consisting of:

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light chain, and progeny homozygous for said modified genome;

first and second parents heterozygous for a genome modified to be incapable of producing an endogenous immunoglobulin heavy chain, and progeny homozygous for said modified genome;

a first parent heterozygous for a genome modified to be incapable of producing an endogenous immunoglobulin light chain, a second parent heterozygous for a genome modified to be incapable of producing an endogenous immunoglobulin heavy chain and progeny heterozygous for said modified genome so as to be incapable of producing endogenous immunoglobulin heavy and light chains;

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobuin light and heavy chains, and progeny homozygous for said modified genome;

a first parent hemizgyous for a genome modified to be capable of producing xenogeneic immunoglobulin heavy chain, a second parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains, and progeny heterozygous for said modified genome so as to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for a modified genome so as to be capable of producing xenogeneic immunoglobulin heavy chain;

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin heavy chain, and progeny 1) homozygous for said modified genome and 2) homozygous for said modification of being incapable of producing endogenous immunoglobulin light and heavy chains and also hemizygous for the modification of being capable of producing xenogeneic immunoglobulin heavy chain;

a first parent hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light chain, a second parent heterozygous for a genome modified to be incapable of producing immunoglobulin heavy and light chains, and progeny heterozygous for said genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for said genome modified to be capable of producing xenogeneic immunoglobulin light chain;

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light chain, and progeny 1) homozygous for said modified genome and 2) homozygous for said modification of being incapable of producing endogenous immunoglobulin light and heavy chains and also hemizygous for the modification of being capable of producing xenogeneic immunoglobulin light chain;

a first parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for xenogeneic immunoglobulin heavy chain, a second parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for the modification of being capable of producing xenogeneic immunogobulin light chain, and progeny homozygous and heterozygous for said genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for the modification of being capable of producing xenogeneic immunoglobulin light and heavy chains,

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizgyous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny 1) homozygous for said modified genome, and 2) homozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy and light chains and hemizygyous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains;

first and second parents homozygous for a genome modified to be incapable of producing endogenous immunoglobulin light and heavy chains and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny homozygous for said modified genome;

a first parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain, a second parent hemizygyous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain and hemizygyous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains;

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain and hemizygous for a genome modified to be capable of producing xenogeneic immunglobulin light and heavy chains, and progeny 1) homozygous for said modified genome and 2) homozygous for a genome modified to be incapable of producing endogenous immunoglobulin heavy chain and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains;

a first parent heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light chain, a second parent hemizygyous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light chain and hemizygyous for a genome modified to be capable of producing xenogeneic immunoglboulin light and heavy chain; and

first and second parents heterozygous for a genome modified to be incapable of producing endogenous immunoglobulin light chain and hemizgyous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains, and progeny 1) homozygous for said modified genome, and 2) homozygous for a genome modified to be incapable of producing endogenous immunoglobulin light chain and hemizygous for a genome modified to be capable of producing xenogeneic immunoglobulin light and heavy chains.

73. A method according to Claim 72, wherein said modification of a genome so as to be incapable of producing endogenous immunoglobulin light and/or heavy chain is inactivation of the endogenous immunoglobulin loci as a result of homologous recombination.

74. A method according to Claim 73 wherein said inactivation is a result of introduction of a lesion into the endogenous immunoglobulin loci.

75. The genetically modified non-human animal produced by the method according to Claim 72.

76. The animal according to Claim 75, wherein the animal is a rodent.

77. The animal according to Claim 76 wherein the animal is a murine animal.

78. The animal according to Claim 75, wherein the xenogeneic immunoglobulin is human immunoglobulin.